REMARKS

Claims 1, 36, and 42 have been amended. Claims 27, 46, 50-56, 69-70, 75, and 79 have been cancelled. New claims 80-93 have been added. Claims 1, 11, 34, 36, 42, 43, and 80-93 are pending in the present application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance.

I. Restriction Requirement

The Office Action imposed restriction and election requirements. Specifically, Applicants were requested to elect one of eleven designated groups under 35 U.S.C. § 121.

As provided therein, Applicants provisionally elected with traverse the claims of Group I. Claims 1, 11, 27, 34, 36 and 42-43 read on the elected subject matter.

Applicants were also required to identify a single gene or nucleic acid to be searched. Applicants selected the gene *yerQ* with accession number BG12843.

Applicants confirm this election. Claims 46, 50-56, 69-70, 75, and 79 have been cancelled. Applicants reserve the right to file continuing applications directed to the non-elected subject matter.

II. The Rejection of Claims 1, 11, 27, 34, 36, 42, and 43 under 35 U.S.C. § 112, First Paragraph

Claims 1, 11, 27, 34, 36, 42, and 43 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action stated:

> The instant specification and claims are encompassing currently unidentified nucleic acid molecules and claiming that these nucleic acids have the capability of hybridizing to a plurality of nucleic acids sequences. Therefore, there is evidence that claimed nucleic acids have not yet been identified. Moreover, the instant specification fails to disclose the specific nucleic acid molecules; rather the specification broadly defines the sequences to be any nucleic acid molecule of a *Bacillus subtilis* origin, without any discretion. In view of the lack of evidence, it is apparent that Applicants were not in possession of all or many nucleic acid molecules in the presence of at least one subinhibitory amount of an antimicrobial compound having an unknown mode of action, that hybridize with a plurality of nucleic acid sequence corresponding to genes of the bacterial cells at the time of filing the instant application. The specification and claims lack

> sufficient written description of the generically claimed isolated nucleic acid molecule of a *Bacillus subtilis* origin comprising a nucleotide sequence capable of hybridizing to a nucleotide sequence. The specification does not place any structural, chemical or absolute functional limitations on the nucleic acid molecule per se. The recitation of a nucleic acid sample does not convey a common structure or function. The scope of the claims includes numerous structural variants and the genus is highly variant because a significant number of structural differences between the genus members are permitted. The specification fails to provide guidance on the structure of the nucleic acid samples. Structural features that could distinguish molecules in the genus from others in the class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed.

This rejection is respectfully traversed.

Applicants submit that the specification complies with the written description requirement.

The Office asserts that the instant specification and claims encompass currently unidentified nucleic acid molecules and, therefore, there is evidence that claimed nucleic acids have not yet been identified and that Applicants were not in possession of all or many nucleic acid molecules in the presence of at least one subinhibitory amount of an antimicrobial compound having an unknown mode of action, that hybridize with a plurality of nucleic acid sequence corresponding to genes of the bacterial cells at the time of filing the instant application.

As set forth in Federal Circuit decisions, a specification complies with the written description requirement if it provides "a precise definition, such as by structure, formula, chemical name, or physical properties of the claimed subject matter sufficient to distinguish it from other materials." See, e.g., *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997); *Enzo Biochem v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002).

The test is <u>not</u> whether one of ordinary skill in the art envisions all of the claimed subject matter. The Federal Circuit has held that, "It is not correct ... that all functional descriptions of genetic material fail to meet the written description requirement." *Enzo Biochem v. Gen-Probe Inc.*, 63 U.S.P.Q.2d at 1613.

Applicants respectfully point out that the claimed invention is directed to methods for determining the mode of action of an antimicrobial compound by identifying specific genes affected by the antimicrobial compound through hybridization relative to various standards with known modes of action. For example, if chloramphenicol is the standard antimicrobial

compound, a signature of *Bacillus subtilis* genes which are up-regulated and/or down-regulated will be generated. If the antimicrobial compound has the same mode of action as chloramphenicol, it will generate a similar signature profile as chloramphenicol. Tables 4-23 show the signature profiles of genes from *Bacillus subtilis* that are regulated by chloramphenicol (Example 8), ciprofloxacin (Example 9), cephalothin (Example 10), norfloxacin (Example 11), vancomycin (Example 12), streptomycin (Example 13), gentamicin (Example 14), erythromycin (Example 15), munumbicin B (Example 16), trimethoprim (Example 17), and rifampin (Example 18). It is important to note that the signature profile of genes affected by a particular standard antimicrobial compound with a known mode of action may include some genes whose function is unknown. It is the overall signature of genes regulated by the compound that is important.

The Office asserts that the instant specification fails to disclose the specific nucleic acid molecules; rather the specification broadly defines the sequences to be any nucleic acid molecule of a *Bacillus subtilis* origin, without any discretion. Applicants disagree. The plurality of nucleic acid sequences corresponding to genes of *Bacillus subtilis* cells is disclosed on page 13, line 1, to page 14, line 36, of the specification. The specification provides that the nucleic acids can be the genes or fragments thereof described by Kunst *et al.*, 1997, *Nature* 390: 249-256 (attached). Kunst *et al.* describe the complete genomic sequence of *Bacillus subtilis* strain BGSC1A2. Moreover, the plurality of nucleic acid sequences corresponding to genes of *Bacillus subtilis* cells can be selected from the groups of genes disclosed in Tables 4-23 of the specification or fragments thereof. Furthermore, Example 4 describes amplification of the protein coding ORFs from *Bacillus subtilis* BGSC1A2 genomic DNA using a complete set of *Bacillus subtilis* ORF-specific PCR primers from Eurogentec (Seraing, Belgium).

Since the plurality of nucleic acid sequences correspond to genes of *Bacillus subtilis* cells, as described above, detecting hybridization complexes formed by contacting at least one nucleic acid sample, obtained by culturing cells of the *Bacillus subtilis* in the presence of at least one sub-inhibitory amount of an antimicrobial compound having an unknown mode of action, with the plurality of nucleic acid sequences, the hybridization complexes correspond to the genes of the *Bacillus subtilis* cells. The presence, absence, or change in the amount of the hybridization complexes detected, compared with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells cultured in the absence or presence of a standard compound having a known mode of action, is indicative of the similarity or dissimilarity of the mode of actions of the antimicrobial

compound and the standard compound. Standard antimicrobial compounds having known modes of action are described on page 7, line 4, to page 11, line 5, of the specification.

The Office also asserts that the specification fails to provide guidance on the structure of the nucleic acid samples. Nucleic acid samples are defined on page 12, lines 5-34, of the specification. The nucleic acid samples are obtained by cultivating *Bacillus subtilis* cells at sub-inhibitory doses with a test antimicrobial compound over a defined time course. One of ordinary skill in the art would understand that the structure of the nucleic acids in the nucleic acid samples are the same as the plurality of nucleic acid sequences corresponding to genes of *Bacillus subtilis* cells described above

The Office suggests that in the absence of an isolated nucleic acid molecule ... hybridizing to a plurality of sequences described only by its ability to hybridize fails to meet the written description requirements because a precise definition, such as by structure, formula, chemical name, or physical properties, is required. Applicants disagree that hybridization is merely functional. Applicants submit that hybridization is a structural feature. The structural feature of hybridization under specific stringency conditions has been used for decades by persons of ordinary skill in the art to determine the relatedness of genes and their encoded products with respect to structure and function to ascertain whether they belong to the same genus or family. The scientific literature abounds with disclosures of hybridization as a structural feature to describe the primary structure and relatedness of genes as well as to distinguish a gene from other genes. Moreover, as mentioned above, the nucleic acid sample is derived from the same *Bacillus subtilis* cells as the plurality of nucleic acid sequences.

Applicants have recited a representative number of nucleic acids falling within the scope of the claims such that the skilled artisan would be able to use the nucleic acids for their intended purpose and would be able to reasonably predict the structure of the claimed nucleic acids. A skilled artisan would not be required to *de novo* locate, identify and characterize the claimed method. Therefore, the claims meet the written description requirements.

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 112 and respectfully request reconsideration and withdrawal of the rejections.

III. The Rejection of Claims 1, 11, 27, 34, 36, 42, and 43 under 35 U.S.C. § 112, Second Paragraph

Claims 1, 11, 27, 34, 36, 42 and 43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on two grounds.

Ground 1: The Office Action states that the terms "sub-inhibitory amount" and "similarity or dissimilarity" in claim 1 are relative terms which render the claim indefinite because the terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.. This rejection is respectfully traversed.

The Office asserts that the terms "sub-inhibitory amount" and "similarity or dissimilarity" are indefinite because they are not described in the specification. Applicant respectfully points out that this in incorrect. The term "sub-inhibitory amount" is defined on page 11, line 35, to page 12, line 3, of the specification. The term "similarity or dissimilarity" is defined on page 22, line 16, to page 23, line 2, of the specification.

Ground 2: The Office Action states that the term "significantly different" in claim 36 is a relative term which renders the claim indefinite because he term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. This rejection is respectfully traversed.

The Office also asserts that the term "significantly different" is indefinite because it is not described in the specification. Applicant respectfully points out that this is incorrect. The term "significantly different" is defined on page 23, lines 15-22, of the specification.

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 112 and respectfully request reconsideration and withdrawal of the rejections.

IV. The Rejection of Claims 1, 11, and 27 under 35 U.S.C. § 102(b)

Claims 1, 11 and 27 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Zhang *et al.* (*Gene* 255: 297-305, 2000). The Office Action stated:

> Zhang *et al.*, teach a method for determining the mode of action of an antimicrobial compound, comprising: a detection of hybridization complexes from *Bacillus subtilis,* a comparison of the hybridization complexes to a standard compound having a known mode action, and assigning a mode of action for the unknown antimicrobial compound based on the similarity or dissimilarity of values assigned to the hybridization complexes detected from the known sample.

This rejection is respectfully traversed.

Under the standard required for anticipation under 35 U.S.C. § 102, the cited prior art reference is required to disclose every element of the claimed invention. *Lewmar Marine Inc. v. Barient Inc.*, 3 USPQ2d 1766 (Fed. Cir. 1987).

Zhang *et al.* disclose that three regulated promoter systems, previously developed in *Bacillus*, all function and exhibit titratable induction in *Staphylococcus aureus*, which together provide physiologically relevant protein expression levels of over three orders of magnitude. Zhang *et al.* also disclose that the chromosomally-integrated Spac system, in combination with the LacI-expressing plasmid pFF40, provides an inducible, titratable and well-regulated system for testing the requirement of specific gene products for cell viability and creating conditional lethal phenotypes in *S. aureus*. Zhang *et al.* further disclose that strains with titratable gene products are useful for linking the antibacterial activity of an antibiotic with the proposed target mechanism. However, Zhang *et al.* do not describe a method for determining the mode of action of an antimicrobial compound in a *Bacillus subtilis* cell, as claimed in the instant application.

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 102(b) and respectfully request reconsideration and withdrawal of the rejections.

V. The Rejection of Claims 1, 11, 34, 36, and 42-43 under 35 U.S.C. § 102(b)

Claims 1, 11, 34, 36 and 42-43 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Wilson *et al.* (*PNAS USA* 96: 12833-12838, 1999). The Office Action stated:

> Wilson *et al.*, teach a method for determining the mode of action of an antimicrobial compound, comprising: a detection of hybridization complexes, a comparison of the hybridization complexes to a standard compound having a known mode action, and assigning a mode of action for the unknown antimicrobial compound based on the similarity or dissimilarity of values assigned to the hybridization complexes detected from the known sample.

This rejection is respectfully traversed.

Under the standard required for anticipation under 35 U.S.C. § 102, the cited prior art reference is required to disclose every element of the claimed invention. *Lewmar Marine Inc. v. Barient Inc.*, 3 USPQ2d 1766 (Fed. Cir. 1987).

Wilson *et al.* disclose exploring drug-induced alterations in gene expression in *Mycobacterium tuberculosis* by microarray hybridization. However, Wilson *et al.* do not describe a method for determining the mode of action of an antimicrobial compound in a *Bacillus*

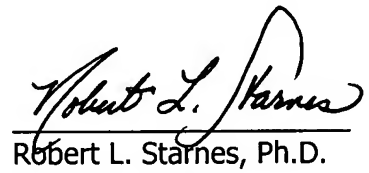
substilis cell, as claimed in the instant application.

For the foregoing reasons, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 102(b) and respectfully request reconsideration and withdrawal of the rejections.

VI. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,



Date: August 31, 2006

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